

# Consensus Statement on The Use of Fractional Exhaled Nitric Oxide (FE<sub>NO</sub>) in the Clinical Management of Asthma

National Jewish Health | December 2009

## Consensus Meeting at National Jewish Health

The following White Paper presents points of clinical consensus arrived at by participants in a closed meeting held at National Jewish Health in Denver, Colorado. The meeting took place on July 20, 2009. The group of clinicians and researchers, all leaders in the field of asthma, met to discuss the utility of FE<sub>NO</sub> in the diagnosis and management of asthma. The following represents a summary of their presentations, discussions and recommendations.

This meeting was funded by an unrestricted educational grant from Aerocrine.

### Moderator:

David Tinkelman, MD

National Jewish Health, Denver, CO

### Presenters:

Peter Boggs, MD

The Asthma Allergy Clinic, Shreveport, LA

Neal Jain, MD

Dean Health System, Madison, WI

Miguel Lanz, MD

AAADRS Clinical Research Center, Coral Gables, FL

Stanley Szefer, MD

National Jewish Health, Denver, CO

### Discussants:

Kaiser Lim, MD

Mayo Clinic, Rochester, MN

Andrew Liu, MD

National Jewish Health, Denver, CO

Harold Nelson, MD

National Jewish Health, Denver, CO

Jeffrey Rosch, MD

Penn State Milton S. Hershey Medical Center, Hershey, PA

## Executive Summary and Panel Recommendations

FE<sub>NO</sub> is a good surrogate marker for eosinophilic inflammation, which is associated with steroid responsiveness. FE<sub>NO</sub> significantly correlates with bronchial hyperresponsiveness, bronchodilator reversibility and atopy. In addition to assisting in predicting steroid responsiveness, measurement of FE<sub>NO</sub> can help distinguish asthma from other respiratory conditions, is reproducible and is associated with other markers of asthma severity. It is also a useful measure to monitor adherence to inhaled corticosteroids and to assist in optimizing the dose of inhaled corticosteroids (ICS) to obtain both symptom and inflammation control.

### ***This expert panel recommends:***

1. FE<sub>NO</sub> measurement should be a part of the clinical management of asthma in ambulatory settings in conjunction with other conventional methods of asthma assessment.
2. FE<sub>NO</sub> should be used to determine the presence or absence of eosinophilic airway inflammation, to determine the likelihood of steroid responsiveness, to measure response to steroid therapy and level of inflammation control. In addition, FE<sub>NO</sub> is a useful tool to monitor patient ICS treatment adherence and allergen exposure. Due to phenotypic distinctions and variability in the underlying pathology of asthma, FE<sub>NO</sub> should not be the sole determinant of asthma diagnosis.
3. While standards exist for normal and elevated FE<sub>NO</sub> levels, the benefit of following FE<sub>NO</sub> levels can be enhanced by comparing levels in each individual to their baseline for each individual rather than compared to others in the community, due to wide inter-patient variability and imprecise reference norms.
4. When interpreting the results of FE<sub>NO</sub> clinicians should be familiar with associated variables that can affect FE<sub>NO</sub> readings, such as race, smoking status, a diet high in nitrates, etc.

## Personalizing Asthma Care

Asthma is a common clinical syndrome that involves multiple disease processes. It is highly variable in its underlying pathology, clinical manifestations, natural history and responses to treatment.<sup>1</sup> The development of asthma is based on complex interactions between host factors, particularly genetic, and environmental exposures, such as airborne allergens and viral respiratory infections, that can occur during varied times of an individual's life. The symptoms and progression of asthma involve a highly variable interaction between bronchial hyperresponsiveness, airflow obstruction, and the underlying airway inflammation that stems from reactions between various cell types and mediators. While inflammation in asthma is now well established as the primary target for treatment, variability in the patterns of inflammation suggests phenotypic distinctions that can impact disease presentation and treatment response.

## FE<sub>NO</sub>, Asthma, and Personalized Medicine

According to the Foundation for the National Institutes of Health Biomarkers Consortium, biomarkers are "characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention."<sup>3</sup> The most useful biomarkers are those with the most direct relationship between the marker and the central pathobiological characteristics of a disease process. Ideal biomarkers for asthma should serve to identify the different underlying pathophysiologic features of the disease in individual patients, thus suggesting a targeted course of treatment. New biomarkers for asthma should meet the following criteria:

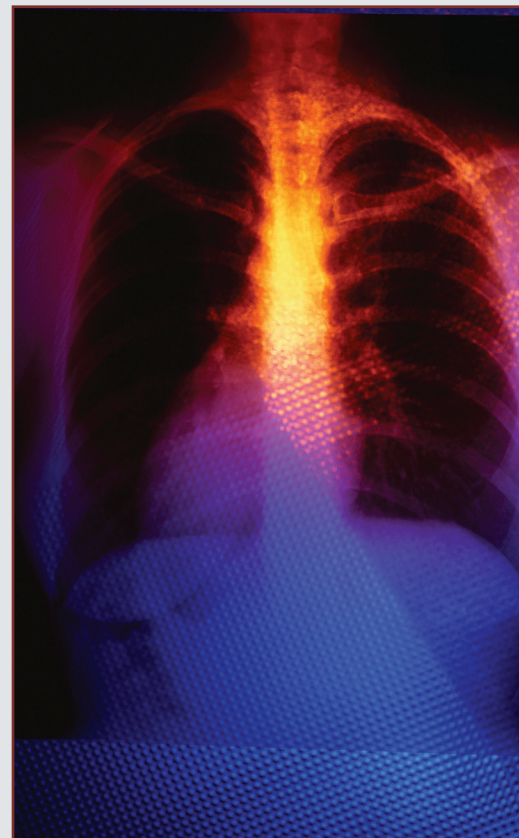
- They must be easily accessible.
- They must be validated in measurement and application.
- They must be easy to measure in the clinical setting.
- They could be combined with other biomarkers to define a specific feature of the disease or cell activity.
- They should address an area of clinical assessment that will improve asthma management.
- They must be cost effective.

## PERSONALIZED MEDICINE

As phenotypes for asthma become better defined, individualized treatment approaches based on genetics and the measurement of biomarkers are likely to develop.<sup>2</sup> Such approaches come under the rubric of "personalized medicine."

The approach to personalized medicine emphasizes the following:

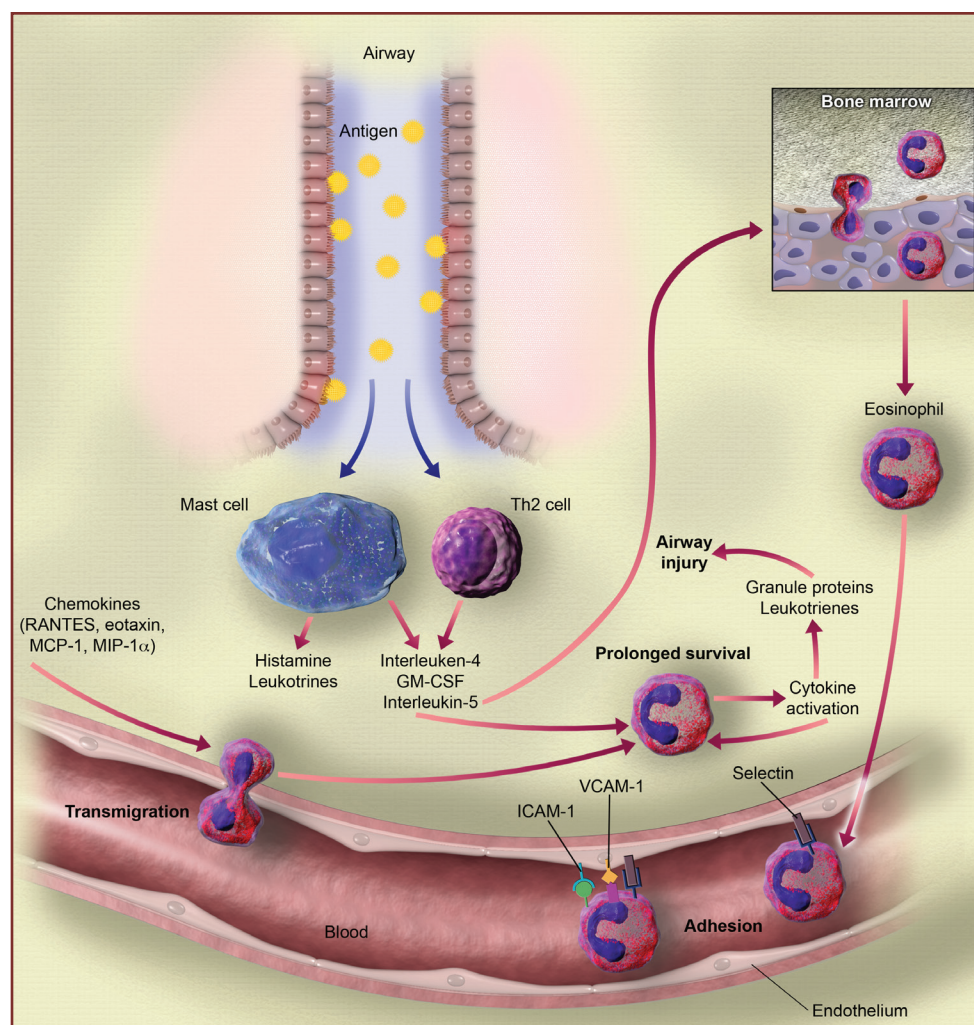
- **Early diagnosis to prevent unnecessary morbidity or mortality associated with the disease.**
- **Prediction of the severity and prognosis for the individual.**
- **Determination of the optimal treatment approach for the individual.**
- **Establishment of appropriate monitoring tools to evaluate therapy.**



Genetic polymorphisms, measurements of inflammatory mediators, sputum analysis, measures of airway hyperresponsiveness, and lung function measures, such as peak expiratory flow and FEV<sub>1</sub>, have been postulated as biomarkers in asthma, although only lung function measurement is routinely performed clinically. Amongst those on the list, some are difficult to obtain and measure and are potentially costly. Since inflammation is a unifying characteristic that underlies the symptoms and disease processes associated with asthma, there is a need for reliable biomarkers that can measure and monitor the existence and changes in inflammation.<sup>4</sup> The opportunity to assess a patient's airway inflammation through the measurement of FE<sub>NO</sub> represents a paradigm shift in asthma care. Airway inflammation is well established as the underlying physiological characteristic of the disease, yet clinicians

treating the disease have previously only been able to infer inflammation by observation of its deleterious results, such as asthma symptoms, overreliance on beta-agonists and abnormal pulmonary function tests.

Nitric oxide (NO) is produced in the airway and is detectable in the exhaled breath. In the human body, NO is biosynthesized by nitric oxide synthase (NOS) enzymes. NOS2A, the inducible NOS isoform implicated in asthma, is predominantly produced in the epithelial cells of the bronchial wall. Release of NO is minimal in normal epithelial cells, but NOS2A overproduces NO in the epithelial cells in the presence of eosinophilic inflammation. Abnormally high levels of FE<sub>NO</sub> can be seen when inflammation is present, and FE<sub>NO</sub> readings are typically elevated in people with asthma, specifically, those with eosinophilic asthma.<sup>5,6</sup>



**Figure 1.** Excess numbers of eosinophils are in the airways of most asthmatics. They contain inflammatory enzymes, generate leukotrienes, and express a wide variety of pro-inflammatory cytokines. [National Heart, Lung, and Blood Institute and the National Asthma Education and Prevention Program. Expert Panel Report (EPR 3): Guidelines for the Diagnosis and Management of Asthma.<sup>2</sup>]



## Eosinophils in Asthma

Eosinophils are not typically found in significant numbers in healthy lung tissue.<sup>7</sup> However, the presence of eosinophils in the lung is a hallmark pathological characteristic of asthma, and the bronchial inflammation that is characteristic of asthma tends to be eosinophilic in nature in most patients [Fig. 1]. Increased numbers of eosinophils are also found in the tissue, blood and bone marrow of most asthmatics, reflecting the presence of systemic inflammation. A large number of studies have confirmed that increased numbers of eosinophils in the blood, sputum, and bronchoalveolar lavage correlate with asthma disease severity measures, such as pulmonary function testing and airway hyperresponsiveness (AHR). Eosinophils are believed to release inflammatory mediators locally, and have been implicated in AHR, goblet cell metaplasia and mucin secretion, smooth muscle hypertrophy and hyperplasia and other aspects of asthma pathology.<sup>8</sup>

As noted, not all asthmatics have eosinophilic airway inflammation. When eosinophilic airway inflammation is present, patients have a better response to steroids.  $FE_{NO}$  levels significantly correlate with the presence or absence of eosinophilia, as found in induced sputum, biopsies, and bronchoalveolar lavage, and thus, may have a role as a surrogate marker for eosinophilic inflammation. This is important in the consideration of the use of  $FE_{NO}$ .

Eosinophil counts in induced sputum and  $FE_{NO}$  can both serve as direct biomarkers for asthma inflammation in the lungs. These biomarkers are advantageous in that they tend to remain elevated even when patients are asymptomatic, and decrease in the presence of ICS. Sputum induction is safe and reproducible, though it is a semi-invasive procedure which cannot be successfully accomplished in up to 13% of adult patients with asthma, and even in a greater percentage of children.<sup>4</sup> Furthermore, for a variety of reasons, it is not ideally situated for use in routine non-academic clinical practice. The technique of measuring  $FE_{NO}$ , in contrast, is non-invasive and well-tolerated.  $FE_{NO}$  measurements are instantaneous, thus, facilitating decision-making at the point of care.

## Challenges in Asthma Care

For many patients and the physicians who treat them, the control of asthma has remained elusive across the entire range of severity. In one large one-year study, total control was only achievable for 40% of asthmatics using GINA and NAEPP guidelines.<sup>9</sup>

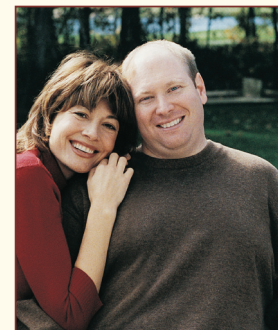
**$FE_{NO}$  levels significantly correlate with the presence or absence of eosinophilia, as found in induced sputum, biopsies, and bronchoalveolar lavage, and thus may have a role as a surrogate marker for eosinophilic inflammation.**

Additionally, there are subsets of patients with asthma which are interchangeably referred to as “steroid-resistant,” “severe refractory asthma,” or simply as having “severe” asthma, which have a significant risk of asthma-related morbidity and mortality.<sup>10,11</sup> The quality of life for those in these subsets is impacted far more than those with less severe forms of the disease, particularly if their asthma remains uncontrolled.<sup>12</sup> Although they account for approximately 10% of all asthmatics, patients with more severe asthma experience the vast majority of asthma morbidity, mortality and costs.<sup>13-16</sup> In fact, an estimated 50% to 60% of all asthma deaths occur in this population despite its small overall number.<sup>17,18</sup> Treatment costs are up to three times as high for these patients, even higher if exacerbations occur.<sup>19,20</sup>

Noneosinophilic asthma is a subtype of severe asthma that is known to be less responsive to steroid therapy. This is problematic in light of current asthma guidelines, which stipulate ICS as the gold standard for treatment. Patients with noneosinophilic asthma may receive increasing doses of ICS precisely because they are less responsive to the medication, potentially compounding their difficulties with ICS side-effects. Berry et al. compared the immunopathology of eosinophilic and noneosinophilic asthma with normal controls in patients with symptomatic asthma in a study evaluating the responsiveness of these groups of patients to inhaled corticosteroids. In this study, compared with placebo, 8 weeks of treatment with ICS led to a significant difference in methacholine PC20 results in eosinophilic compared with noneosinophilic asthma. Eight weeks of ICS treatment reduced  $FE_{NO}$  values substantially for the eosinophilic group, while no significant change was observed in the noneosinophilic subtypes.<sup>21</sup> This study points to the need to move beyond a one-size-fits-all paradigm in asthma care to a more personalized treatment strategy based on asthma phenotypes, and suggests the role that  $FE_{NO}$  may play in the differentiating process.

## CASE STUDY: A 34-year old man with respiratory symptoms

A 34-year old non-smoking man with a history of allergic rhinitis, acid reflux, and anxiety presents with symptoms of cough, wheeze, nasal congestion, and post-nasal drainage. His symptoms have been ongoing for several weeks and do not respond to albuterol. He uses a nasal steroid and an antihistamine daily for allergic rhinitis. Cough and wheeze occur both day and night, and are not aggravated by activity, although he does note dyspnea with exertion. He previously had been placed on a combination therapy of an ICS and a LABA for asthma. He also stopped taking prescribed acid suppressive therapy (ranitidine and omeprazole) due to bloating. He notes symptoms of heartburn a few times a week. Physical exam is remarkable for obesity, bilateral nasal turbinate edema and a clear/white mucous discharge, as well as for posterior pharyngeal cobblestoning, erythema and mucoid exudate.



Spirometry is performed both before and after administration of 2 puffs of albuterol and in this case a mild obstructive pattern at baseline without significant bronchodilator response is found.

	PRE	POST	% CHANGE
<b>FVC</b>	99%	98%	-1 %
<b>FEV<sub>1</sub></b>	88%	92%	+4%
<b>FEV<sub>1</sub>/FVC</b>	74%	78%	+4%
<b>FE<sub>NO</sub> measurement</b>	<b>10 ppb</b>		

## Assessment

1. Cough and wheeze, with a historical diagnosis of asthma, but without any objective evidence for ongoing airway inflammation that would suggest the patient would benefit from ICS.
2. History of GERD, currently off therapy.
3. Allergic rhinitis with past skin testing confirming sensitivity to dust mites. Ongoing rhinitis symptoms despite nasal steroid and antihistamine therapy.

## Plan

1. Start acid suppressive therapy for GERD and possible GERD underlying non-specific symptoms of cough and wheeze.
2. Continue therapy with a nasal steroid and antihistamine. Recommend nasal saline irrigations.
3. DO NOT start anti-inflammatory therapy for asthma given the objective measurement of FE<sub>NO</sub> at 10ppb which suggests patient would not benefit from such therapy.
4. Consider CT of sinuses to evaluate for ongoing sinus disease that may benefit from antimicrobial therapy.

## Follow-up:

After 1 month, the patient notes significant, albeit incomplete improvement in his respiratory symptoms of cough and wheeze. He is continuing to use his nasal steroid and antihistamine and has also found benefit from nasal saline irrigations. He admits to not using his acid suppressive therapy regularly due to continued side effects and feels this may be responsible for his incomplete response.

## Analysis:

This patient presents with multiple co-morbid conditions which could have contributed to his symptoms of cough and wheeze. Exhaled nitric oxide essentially excluded eosinophilic asthma as the underlying cause for his symptoms. The patient historically had been diagnosed with asthma and demonstrated some obstruction on spirometry with a low ACT score, suggesting that the addition of an ICS would have been the next step. The low FE<sub>NO</sub> resulted in a focus on co-morbid conditions instead. In this case, measurement of FE<sub>NO</sub> played a significant role in preventing an erroneous diagnosis of asthma and a potential escalating course of inhaled steroids. If this therapeutic approach failed to improve the condition for this patient, further evaluation for possible non-eosinophilic asthma might be warranted.

## Clinical Applications of Exhaled Nitric Oxide in the Diagnosis and Management of Asthma

### Predict Steroid Response

$FE_{NO}$  measurements may be used to determine the probable response to ICS in both asthmatics and in patients who present with non-specific respiratory symptoms.

A study by Smith et al. demonstrated the ability of  $FE_{NO}$  measurements to predict steroid response in subjects with persistent, previously undiagnosed non-specific respiratory symptoms when compared to the use of peak flows,  $FEV_1$ , bronchodilator response and airway hyper-responsiveness. The predictive accuracy of  $FE_{NO}$  measurements to identify steroid response was significantly higher than conventional predictors, with the greatest response seen at  $FE_{NO}$  levels > 47 ppb.<sup>22</sup>

Another double-blind, multicenter trial from the NHLBI Childhood Asthma Research and Education (CARE) Network (Szeffler et al.) evaluated responses to ICS (fluticasone) and leukotriene receptor antagonists (montelukast) in asthmatic children. The study also looked at the factors that might determine variability in medication response. Response was defined as improvement in  $FEV_1$  of 7.5% or greater. In this study, 17% of 126 participants responded to both medications, 23% responded to fluticasone alone, 5% responded to montelukast alone, and 55% responded to neither medication. Children who responded to fluticasone had significantly greater mean  $FE_{NO}$  levels at baseline (54 ppb, 95% CI, 19-90) than those who responded to montelukast alone (26 ppb, 95% CI, 21-27) or to neither medication (23 ppb, 95% CI, 10-41).<sup>23</sup>

Both of these studies (Smith and Szeffler) support the use of  $FE_{NO}$  in assessing the potential for patients with asthma to respond to ICS.

### Optimize Therapy Through Early Recognition of Loss of Control

NAEPP guidelines recommend both “step-up” and “step-down” approaches for adjustment of controller medication based on changes in parameters associated with asthma

control, including symptoms, use of beta2-agonists and lung function.<sup>2</sup>  $FE_{NO}$  has the potential to provide further guidance based on knowledge of the state of a patient’s eosinophilic inflammation.

A second outcome demonstrated in the CARE Network trial<sup>23</sup> was asthma control days, defined as days with no daytime or nighttime asthma symptoms, no rescue albuterol for asthma symptoms or peak flow less than 80% of personal best, no asthma health care use and no asthma-related absences from school or work. In a secondary analysis, Zeiger and associates concluded that higher  $FE_{NO}$  levels ( $P = .036$ ), greater albuterol use ( $P = .029$ ), and more positive aeroallergen skin test responses ( $P = .008$ ), in addition to fewer asthma control days at baseline ( $P < .0001$ ) significantly predicted more asthma control days for patients who had a greater response to fluticasone over montelukast.<sup>24</sup> The findings suggest that a decrease in  $FE_{NO}$  with treatment can serve as a response indicator of asthma control.

Physicians are constantly looking for biomarkers that might help in titrating therapy for their asthmatic patients. In the study of 780 asthmatics by Szeffler and the NIAID Inner City Asthma Consortium, the investigators explored whether measurements of  $FE_{NO}$  could enhance the treatment of severe asthma above and beyond the NAEPP guidelines. The primary outcome was days with asthma symptoms.  $FE_{NO}$  monitoring resulted in fewer prednisone bursts, but did not result in a significantly reduced number of days with asthma symptoms, unscheduled visits, and hospitalizations as compared to the guidelines-based treatment alone. However, it should be noted that in this study, long acting beta agonists (LABAs) were used with the ICS and this therapy may have controlled symptoms, but not changed the  $FE_{NO}$  levels or controlled the inflammation. This would potentially explain the improvement in prednisone bursts and the lack of improvement in asthma symptoms in the group managed with the addition of  $FE_{NO}$  monitoring. Post-hoc analyses within various sample strata suggest that  $FE_{NO}$  might enhance the treatment of patients with obesity, high blood eosinophil count, and atopy.<sup>25</sup>



**$FE_{NO}$  measurements may be used to determine the probable response to ICS in both asthmatics and in patients who present with non-specific respiratory symptoms.**

## Monitor Adherence with ICS

Non-adherence to ICS is associated with higher rates of hospitalization and mortality in asthmatics,<sup>26</sup> yet an estimated 50% of patients do not take their long-term control medication as prescribed.<sup>27</sup>

That FE<sub>NO</sub> is effective in signifying non-adherence to ICS is evidenced by a study by Beck-Ripp et al. This group compared exhaled NO to conventional lung function parameters at rest and after exercise during sequential changes of ICS in children with persistent asthma. Treatment compliance was monitored via the dose indicator on the inhalant device. FE<sub>NO</sub> readings were able to differentiate between the randomized groups of children briefly treated with or without steroids, whereas forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) at rest and after exercise could not. Additionally, a positive correlation was established between a drop in FE<sub>NO</sub> levels and medication adherence.<sup>28</sup> This study demonstrates that FE<sub>NO</sub> measurement has the potential to provide early warning of non-adherence, thus enhancing the potential for patient outcomes.

## Monitor Treatment

Exhaled NO monitoring can assist physicians in verifying the effectiveness of ICS treatment for a given patient and in determining the patient's minimal effective dose. A study by Silkoff et al. examined the dose response of increasing doses of inhaled beclomethasone dipropionate (iBDP) on measures of FE<sub>NO</sub>, spirometry, and PC20. A clear dose-dependent relationship was established between changes in doses of iBDP and changes in FE<sub>NO</sub> levels. FE<sub>NO</sub> fell even with the subtherapeutic dose of 100 mg/d of iBDP (**Fig. 2**). In this study, FE<sub>NO</sub> was a better indicator than either FEV<sub>1</sub> or PC20 in establishing a dose response for 100 mcg/d and 800 mcg/d

of iBDP; however, it did not distinguish 100 mg/d from 400 mg/d and 400 mcg/d from 800 mcg/d.<sup>29</sup>

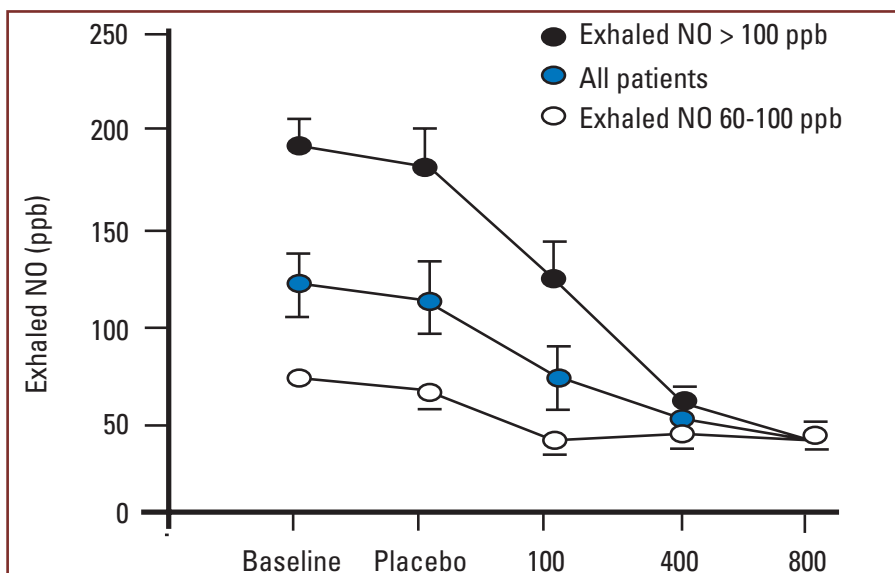
## Assist in the Diagnosis and Management of Childhood Asthma

As in adults, the mainstay of the treatment of persistent asthma in children is ICS. However, a survey of 1,300 parents with children on daily asthma controller medication found that one-third had concerns about their children's use of ICS. Approximately half of those with concerns were specifically troubled about the side effects of the medications, and about one third cited concerns about possible long-term effects.<sup>30</sup> Such attitudes can have a negative impact on treatment adherence and subsequent outcomes, given that it is up to parents to initiate and manage their children's medication regimens.<sup>30</sup>

Patients who see asthma as an occasional or episodic problem are less likely to embrace the use of daily controller medication. Conversely, patients are most apt to accept and utilize ICS when they understand that chronic inflammation underlies the episodic manifestation of obvious symptoms, and that the disease is still there even when symptoms are not obvious.<sup>26</sup> It is certainly possible that evidence of their children's FE<sub>NO</sub> levels can offer parents objective evidence of inflammation and illustrate the need for daily medication, thus boosting adherence and outcomes in childhood asthma.

The diagnosis of asthma in preschool children is usually made on the basis of clinical history. Spirometry requires more cooperation than many young children can manage, and even when usable readings are obtained, lung function measurements are often normal or super-normal. Thus, FE<sub>NO</sub> presents an attractive, non-invasive alternative to spirometry which can be used along with a good history and physical examination.

**Figure 2.** Dose response of the fall in FE<sub>NO</sub> at visits corresponding to baseline, placebo treatment, and then increasing doses of iBDP. The FE<sub>NO</sub> trend for all the subjects (n = 15) is shown together with separate trends for high-baseline (n = 6) and low-baseline (n = 9) FE<sub>NO</sub> groups. FE<sub>NO</sub> at all doses of iBDP was significantly different from placebo treatment, but only FE<sub>NO</sub> levels with 100 mg/d and 800 mg/d of iBDP were significantly different. [Silkoff PE, McClean P, Spino M, Erlich L, Slutsky AS, Zamel N. Dose-response relationship and reproducibility of the fall in exhaled nitric oxide after inhaled beclomethasone dipropionate therapy in asthma patients. *Chest*. 2001;119(5):1322-1328.]





## CASE STUDY: 7-year old girl with asymptomatic asthma

A 7-year old girl was evaluated for food allergies to milk and peanut. She has a history of eczema as an infant and preschool child, and recurrent episodes of wheezing in her first 3 years of life. In the past four years, she has had approximately 2 significant episodes per year of wheezing, for which she uses albuterol and occasionally steroids. She is currently asymptomatic, and reports no symptoms with exercise. Her father denies nasal allergy symptoms. A physical exam is remarkable for allergic shiners, significant inferior turbinate edema. Lungs and skin are normal. Skin tests are positive for ash, maple, Kentucky Blue and timothy grass, dog dander, Alternaria, milk and peanut.



Spirometry is performed both before and after administration of 2 puffs of albuterol, and showed a trivial response.

	PRE	POST	% CHANGE
<b>FVC</b>	107%	110%	+3%
<b>FEV<sub>1</sub></b>	106%	112%	+5%
<b>FEV<sub>1</sub>/FVC</b>	84%	86%	+2%
<b>FEF<sub>25-75</sub></b>	86%	97%	+14%
<b>FE<sub>NO</sub> measurement</b>	<b>56 ppb</b>		

### Assessment

1. Asthma, currently asymptomatic but with significantly elevated FE<sub>NO</sub>.
2. Atopic dermatitis.
3. Allergic sensitization to milk, peanuts and perennial allergens.
4. Consider whether child is at risk for worsening asthma and progressive loss of lung function over time.

### Plan

1. If symptoms increase, begin low-dose ICS therapy.
2. Patient education about allergen exposure and avoidance.

### Analysis

This is a fairly common presentation in pediatrics. Using the measurement of FE<sub>NO</sub> contributed to a better understanding of this patient's allergic condition. Despite her intermittent symptoms, this child has all the risk factors for having persistent childhood asthma (and asthma through adulthood): being female, atopic dermatitis, recurrent wheeze in the first 3 years of life, and allergic sensitization to a perennial allergen. Asthma in childhood is often clinically intermittent. In addition, lung function will often be completely normal especially in children with mild to moderate asthma. The parents in this case were resistant to the diagnosis of asthma and to treatment with an ICS. It is often difficult to convince a parent to use daily controller therapy in the absence of persistent symptoms and normal lung function. However, FE<sub>NO</sub> can help serve as a marker that provides objective evidence of ongoing disease activity, along with other important clinical information. A decision to institute therapy in a child without persistent symptoms needs to be fully supported with as much objective evidence as possible.

## Help Predict Exacerbations

FE<sub>NO</sub> measurements can help predict relapses in patients who currently use or have discontinued ICS and can serve as input to both clinical and parental decisions about increasing, decreasing or discontinuing medication.

In acute exacerbations of asthma, the airways narrow in response to exposure to a variety of stimuli, including allergens or irritants. The intensity of the bronchoconstriction response is related to underlying airway inflammation which can be inferred from FE<sub>NO</sub>. Airway inflammation is thought to occur before changes in lung function in patients with asthma symptoms, thus FE<sub>NO</sub> may be an early indicator for approaching exacerbations. Some patients who appear to have good asthma control as evidenced by their symptoms and quality of life, and even some patients with intermittent asthma, are at risk for exacerbations that are severe and even life-threatening. Monitoring a patient's FE<sub>NO</sub> level, especially when combined with standard measures, such as FEV<sub>1</sub>, may help predict future exacerbations. Gelb et al. reported that patients with elevated FE<sub>NO</sub> (>28 ppb) and FEV<sub>1</sub> <76% predicted had an 85% chance of an exacerbation over a period of 18 months. In contrast, patients who had a combined FEV<sub>1</sub> >76% predicted and FE<sub>NO</sub> < 28 ppb had 0% probability of an asthma exacerbation during the same period.<sup>32</sup> In another study, Pijnenburg et al. showed that in children where ICS were being discontinued and who were about to relapse, had significantly higher mean FE<sub>NO</sub> levels than those who did not.<sup>33</sup> The study demonstrates the potential of FE<sub>NO</sub> as an objective tool to predict relapses in patients who currently use or have discontinued ICS.

## Identify Comorbid Conditions that Underlie Non-specific Respiratory Symptoms

A great number of conditions mimic asthma. Symptoms of cough, wheezing or dyspnea can be caused by the following:

- Acute respiratory illness
- Vocal cord dysfunction
- Allergic rhinitis and sinusitis
- Gastroesophageal reflux disease (GERD)
- Medications, such as ACE inhibitors
- Tracheobronchitis associated with respiratory viral infection or cystic fibrosis
- Congestive heart failure and pulmonary embolism
- Chronic lung diseases (eg, sarcoidosis causing endobronchial granuloma formation)
- Heart disease<sup>2,34</sup>

One of the most promising uses for FE<sub>NO</sub> measurement lies in its potential to assist clinicians in distinguishing asthma from other respiratory and non-respiratory conditions. In particular, low FE<sub>NO</sub> levels imply the absence of eosinophilic airway inflammation and give the clinician insight into whether ICS therapy is likely to be helpful. Low levels of FE<sub>NO</sub> may be more informative in minimizing diagnostic likelihoods than high levels, which can result from multiple causes.

Chronic cough is a frequent presentation in the outpatient setting. A study by Chatkin and colleagues examined the role of FE<sub>NO</sub> in the investigation of chronic cough and found patients with chronic cough not attributable to asthma showed a low FE<sub>NO</sub> value as compared with healthy subjects and asthmatics.<sup>35</sup>

## Limitations in Using the FE<sub>NO</sub> in Clinical Practice

### Monitoring Noneosinophilic Asthma

FE<sub>NO</sub> may represent a crucial tool in distinguishing eosinophilic asthma from noneosinophilic asthma and in selecting therapeutic agents accordingly. However, it is unlikely to be a useful biomarker for monitoring noneosinophilic asthmatics.

### Other Determinants of FE<sub>NO</sub> can Skew Values

Eosinophilic inflammation, respiratory symptoms and atopy are not the only determinants of FE<sub>NO</sub>, and other determinants continue to be investigated. Comorbid conditions, medications, recent consumption of alcohol and tobacco products and certain foods, exercise, and spirometric maneuvers can cause variation in FE<sub>NO</sub> levels. FE<sub>NO</sub> levels are also positively associated with height and age in children.<sup>36</sup> Ethnicity also appears to influence FE<sub>NO</sub> values, as evidenced by a recent study that found that Chinese school children and African-American adults have higher levels than their white counterparts.<sup>37,38</sup> The manufacturer's guidelines for interpretation may not capture the variables that influence FE<sub>NO</sub> levels at a high enough level of sensitivity to allow for reliable use by non-specialists unfamiliar with the clinical literature, though many primary care physicians are already measuring FE<sub>NO</sub> in clinical practice. Elevated FE<sub>NO</sub> levels must not be taken as definitive evidence of asthma, as with normal spirometry, nor, must low FE<sub>NO</sub> levels rule it out.

### Technical Capabilities

As in any clinical test that is used to guide diagnostic and therapeutic decisions, it is important to be confident that the individuals administering the study and evaluating the results of the tests are familiar with the correct procedures. Attention to

**Table 1. Factors affecting FE<sub>NO</sub> levels**

<b>Elevated FE<sub>NO</sub></b>	<ul style="list-style-type: none"> <li>• Airway infection<sup>34</sup></li> <li>• Allergic rhinitis<sup>40</sup></li> <li>• Nitrate-rich diet<sup>41</sup></li> <li>• Bronchodilator<sup>42</sup></li> </ul>
<b>Reduced FE<sub>NO</sub></b>	<ul style="list-style-type: none"> <li>• Spirometric maneuvers<sup>43</sup></li> <li>• Exercise<sup>44</sup></li> <li>• Alcohol consumption<sup>45</sup></li> <li>• Bronchoconstriction<sup>46</sup></li> <li>• Ciliary dyskinesia<sup>47</sup></li> <li>• Pulmonary hypertension<sup>48</sup></li> <li>• Cystic fibrosis<sup>47</sup></li> <li>• Smoking<sup>49</sup></li> <li>• ICS therapy<sup>50</sup></li> </ul>

Adapted from Taylor (Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax*. 2006;61(9):817-27.)

the manufacturer's description and recommendations should be taken. Special care should be taken with children 7 years and younger, since current portable devices use a 6 second stable flow exhalation that may be difficult for them to execute. Some clinicians may wish to implement a policy of measuring FE<sub>NO</sub> only in those 8 years and older. This excludes an important population for whom FE<sub>NO</sub> could otherwise provide valuable information, especially since young children may not be able to provide adequate spirometry results.

### Reimbursement Currently Remains Problematic

Although a CPT code was introduced in 2007, code 95012 ("nitric oxide expired gas determination for measurement of exhaled nitric oxide (NO)"), payor resistance is still common, and some insurance carriers continue to refuse reimbursement for FE<sub>NO</sub> testing on the grounds that it is investigational, experimental or unproven. However, the consensus panel disagrees with this stand, and believes that the data support the use of FE<sub>NO</sub> in asthma management in conjunction with conventional tools. In many cases, the refusal for payment has been based on studies that failed to demonstrate improved outcomes in asthma management, without acknowledgement of other clinical utilities supported by the literature and clinical experience.

### FE<sub>NO</sub> in Scientific Research

By providing an objective, easily-obtained marker for eosinophilic inflammation, FE<sub>NO</sub> has already proven its potential as a reliable surrogate for inflammation in clinical trials of asthma. One promising area of research is related to the use of LABAs, which while known to lack significant inflammatory properties, are often used as monotherapy for asthma. The use of FE<sub>NO</sub> measurements is helping to better understand that patients treated with LABAs and who are uncontrolled by ICS,

are at greater risk for exacerbations than those treated with increased ICS doses. Their exacerbations are more likely to be dependent on inflammation, where as symptoms of wheezing and cough may be more related to the degree of obstruction.

In addition to further investigation of its role in the clinical management of asthma, another promising area for FE<sub>NO</sub> in research is in the diagnosis and management of primary ciliary dyskinesia, which is correlated with low FE<sub>NO</sub> levels.<sup>47</sup>

### Summary

This panel of experts in the management of asthma clearly agrees that FE<sub>NO</sub> meets the standard for a biomarker for asthma as outlined and is a good surrogate marker for eosinophilic airway inflammation, which is associated with steroid responsiveness, bronchial hyperresponsiveness, bronchodilator reversibility and atopy. Its use in clinical practice can play an important role in helping physicians predict and monitor steroid response, monitor adherence, distinguish asthma from other respiratory conditions and help with other markers to better understand asthma severity. While the panel supports the use of FE<sub>NO</sub> measurement in clinical practice, FE<sub>NO</sub> should not be the sole determinant of asthma diagnosis or management, and should never supplant a good history and physical examination. Traditional tools used by the clinician do not correlate well with FE<sub>NO</sub>, hence the FE<sub>NO</sub> value can provide additional valuable information not otherwise apparent to either physician or patient.

The following tables represent consensus suggestions based on clinical experience, for low FE<sub>NO</sub> levels can be used to improve the management of patients with asthma on and off medications.

## Suggested Guidelines for the Use of FE<sub>NO</sub> Measurements in Clinical Practice

**Table 2. Management of steroid-naïve patients with ongoing or recent asthma-like symptoms**

	<b>Normal FE<sub>NO</sub></b> <25 ppb adults <20 ppb children	<b>Intermediate or rising FE<sub>NO</sub></b> 25-50 ppb adults 20-35 ppb children	<b>High FE<sub>NO</sub></b> >50 ppb adults >35 ppb children
<b>Symptomatic</b>	<ul style="list-style-type: none"> <li>• Unlikely to respond to ICS therapy</li> <li>• Consider alternative diagnosis such as: GERD, vocal cord dysfunction, anxiety-hyperventilation, bronchiectasis, primary ciliary dyskinesia, cardiac disease</li> </ul>	<ul style="list-style-type: none"> <li>• May respond to ICS therapy</li> <li>• Based on clinical judgment, consider initiating ICS therapy and monitor change in FE<sub>NO</sub></li> </ul>	<ul style="list-style-type: none"> <li>• Highly likely to respond to ICS therapy, particularly in children</li> <li>• Investigate allergen exposure</li> </ul>
<b>Asymptomatic</b>	<ul style="list-style-type: none"> <li>• Await initiation of ICS therapy; repeat FE<sub>NO</sub> measurement when symptomatic</li> <li>• Based on patient history, consider diagnosis other than asthma</li> </ul>	<ul style="list-style-type: none"> <li>• May respond to ICS therapy; repeat FE<sub>NO</sub> measurement when symptomatic; or</li> <li>• Based on clinical judgment, consider initiating ICS therapy and monitor change in FE<sub>NO</sub></li> </ul>	<ul style="list-style-type: none"> <li>• Address underlying airway inflammation, patient highly likely to benefit from ICS therapy</li> <li>• Consider initiating ICS therapy</li> <li>• Investigate allergen exposure</li> </ul>

Adapted from Taylor (Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax*. 2006;61(9):817-27.)

**Table 3. Management of patients diagnosed with asthma, treated with ICS or ICS/LABA**

	<b>Normal FE<sub>NO</sub></b> <25 ppb adults <20 ppb children	<b>Intermediate or rising FE<sub>NO</sub></b> 25-50 ppb adults 20-35 ppb children	<b>High FE<sub>NO</sub></b> >50 ppb adults >35 ppb children
<b>Symptomatic</b>	<ul style="list-style-type: none"> <li>• Unlikely to respond to increased ICS dose</li> <li>• Consider alternative/comorbid diagnosis: GERD, VCD, anxiety-hyperventilation, bronchiectasis, primary ciliary dyskinesia, cardiac disease</li> </ul>	<ul style="list-style-type: none"> <li>• Potentially uncontrolled airway inflammation</li> <li>• Address treatment adherence</li> <li>• Investigate ICS delivery problems</li> <li>• May benefit from increased ICS dose</li> <li>• Investigate and reduce allergen load</li> </ul>	<ul style="list-style-type: none"> <li>• Address uncontrolled airway inflammation and risk of exacerbation</li> <li>• Address treatment adherence</li> <li>• Investigate ICS delivery problems</li> <li>• Consider increasing ICS dose</li> <li>• Investigate for and reduce allergen exposure</li> </ul>
<b>Asymptomatic</b>	<ul style="list-style-type: none"> <li>• Adequate dosing and good adherence to prescribed therapy</li> <li>• Consider reducing ICS dose</li> </ul>	<ul style="list-style-type: none"> <li>• Potentially uncontrolled airway inflammation</li> <li>• Monitor changes in symptoms and FE<sub>NO</sub> level</li> <li>• Do not reduce ICS unless patient remains asymptomatic with stable FE<sub>NO</sub> level over time</li> </ul>	<ul style="list-style-type: none"> <li>• Address uncontrolled airway inflammation and risk of exacerbations</li> <li>• Do not reduce or withdraw ICS</li> <li>• Investigate for and reduce allergen exposure</li> <li>• Assess for poor perception of symptoms</li> </ul>

Adapted from Taylor (Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax*. 2006;61(9):817-27).



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